DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DEC 10 1992

Wilma F. Bergfeld, M.D.
President
American Academy of Dermatology
1029 Vermont Avenue, N.W., Suite 610
Washington, D.C. 20005-3500

Dear Dr. Bergfeld:

I am writing in response to your letter of October 28, 1992, concerning the Food and Drug Administration's (FDA) review of hydroquinone as an over-the-counter (OTC) skin bleaching active ingredient. In your letter, you state that the American Academy of Dermatology (AAD) believes the available medical evidence demonstrates that OTC 2% hydroquinone skin bleaching drug products are generally safe when used as recommended "to bleach or otherwise lighten limited areas of hyperpigmented skin." AAD recommends that FDA continue to approve OTC hydroquinone skin bleaching drug products, and that the agency require full and correct labeling and promotion of these products. AAD also recommends the inclusion of a warning on OTC skin bleaching drug products to inform the consumer of hydroquinone's potential to cause exogenous ochronosis. While AAD believes the current data are inadequate to implicate topical hydroquinone as a cutaneous carcinogen, AAD encourages continued epidemiologic and basic science research on this subject as well as the association of exogenous ochronosis with the use of hydroquinone.

As you know, in 1982, FDA published a tentative final monograph (proposed rule) for OTC skin bleaching drug products in which it tentatively proposed hydroquinone (1.5 to 2%) as the only active ingredient that was safe and effective for OTC skin bleaching use (copy enclosed). Since that time, the agency has received new information that raises questions concerning the safety of hydroquinone as an OTC skin bleaching drug product. Scientists from our Center for Drug Evaluation and Research (CDER) are currently reviewing: (1) carcinogenicity studies on hydroquinone, (2) the link of hydroquinone (1.5 to 2%) to exogenous ochronosis, and (3) additional data (including labeling) pertinent to the safety of hydroquinone as an OTC skin bleaching drug product.

On February 18, 1992, the agency received a submission from the New York City Department of Consumer Affairs expressing concerns about the recent safety data generated on hydroquinone and the improper labeling and misrepresentation of currently marketed OTC skin bleaching drug products.

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On May 20, 1992, CDER staff met with the Nonprescription Drug Manufacturers Association's (NDMA) Hydroquinone Task Group to discuss the Task Group's research activities concerning the safety of hydroquinone (meeting minutes enclosed). The Task Group discussed hydroquinone's medicinal importance and clinical benefit as an OTC drug and addressed the recent data regarding the safety of hydroquinone as an OTC skin bleaching drug product.

At this meeting, the NDMA Hydroquinone Task Group presented the agency with voluntary labeling guidelines for OTC hydroquinone skin bleaching drug products (copy enclosed). These guidelines are being implemented voluntarily when the next printing of new packaging occurs to provide uniform compliance by industry members of the Hydroquinone Task Group to the proposed FDA regulations outlined in the 1982 tentative final monograph. The guidelines represent a combination of labeling language proposed by the agency and new language proposed by the Hydroquinone Task Group. These guidelines are currently being reviewed by CDER for further suggestions (such as an exogenous ochronosis warning) that may be desirable.

At the agency's request, the NDMA's Hydroquinone Task Group in cooperation with your association is developing a protocol to survey AAD members on the occurrence of hydroquinone-associated exogenous ochronosis in their practices. The agency has recently commented on a draft copy of the survey protocol and looks forward to its implementation shortly. This information should prove valuable in helping the agency to better evaluate the severity of hydroquinone-associated exogenous ochronosis in the United States.

FDA's future policy on OTC hydroquinone skin bleaching drug products is expected to be published in the FEDERAL REGISTER next year. At that time, all interested persons will be invited to submit comments regarding our proposed actions. I have instructed that your letter be included in the administrative record for the agency's current rulemaking for OTC skin bleaching drug products.

Thank you for sharing your comments and concerns with us. We appreciate the Academy's cooperation and participation pertaining to the development and implementation of the ochronosis survey.

Sincerely yours,

Carl C. Peck, M.D.
Director
Center for Drug Evaluation and Research

Enclosures

American Academy of Dermatology

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October 28, 1992

The Honorable David A. Kessler, M.D.
Commissioner
U.S. Food and Drug Administration
Room 14-71, Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

I am writing to you concerning the Food and Drug Administration's (FDA) review of hydroquinone and the revision of the Tentative Final Monograph (proposed rule) entitled, "Skin Bleaching Drug Products for Over-the-Counter Human Use." This document was originally published in the *Federal Register* on September 3, 1982.

Earlier this year, the New York City Department of Consumer Affairs questioned the safety of over-the-counter (OTC) skin bleaching products containing 2% hydroquinone. Hydroquinone has been associated with the relatively rare occurrence of exogenous ochronosis and has been questionably implicated in cutaneous carcinogenesis. This action has prompted the American Academy of Dermatology to reevaluate the available data on this drug.

The available medical evidence demonstrates that OTC products containing no more than 2% hydroquinone are generally safe when used as recommended "to bleach or otherwise lighten limited areas of hyperpigmented skin." For several decades, these products have been widely used in the United States by millions of Americans. Since 1976, there have been only 14 published cases of medically diagnosed ochronosis associated with hydroquinone, and most of these cases occurred in South Africa.

In reviewing the data on hydroquinone, the Academy has become aware that there may have been failures to comply with the proposed regulations outlined in the 1982 Tentative Final Monograph. These shortcomings involved the improper or incomplete labeling and promotion of these products. It is our understanding that the labels of certain hydroquinone products claim that hydroquinone will "even out" or "smooth" skin tone; did not properly and

fully give directions for the application and/or duration of use; failed to indicate the concentration of hydroquinone in the product; did not contain a sunscreen, or if they did, may not have mentioned the strength of the sunscreen; failed to mention that the effects of hydroquinone may not be noticeable when used on very dark skin; and/or failed to mention that hydroquinone may not be effective on certain pigmented skin lesions. We are also aware, however, that in May the Nonprescription Drug Manufacturers Association (NDMA) instituted voluntary labeling guidelines to correct these abuses.

The American Academy of Dermatology recommends that the FDA continue to approve OTC hydroquinone products, and that the agency require full and correct labeling and promotion of these products. The relatively rare occurrence of exogenous ochronosis should be mentioned on the warnings distributed with the product. While we do not believe that there are adequate data to implicate topical hydroquinone as cutaneous carcinogens, the Academy encourages continued epidemiologic and basic science research on this subject as well as the association of exogenous ochronosis with the use of hydroquinone.

I thank you in advance for your time and consideration. If I or the Academy can be of any assistance to you in this matter, I hope that you will not hesitate to contact me.

Sincerely,

Wilma F. Bergfeld, M.D.
President

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

FROM: Director
Monograph Review Staff (HFD-810)

SUBJECT: Material for Docket No. 78N-0065

TO: Dockets Management Branch (HFA-305)

☑ The attached material should be placed on public display under the above referenced Docket No.

☐ This material should be cross-referenced to Comment(s) No. _____.

William E. Gilbertson, Pharm. D.

Attachment

Please send me updated table of contents

Don Dobbs
HFD-820 MPN I
Rm 211